TOTAL EXPOSURE STUDY
BIOMARKERS OF EXPOSURE

Smoke Constituent. Cadmium, Cd [CAS# 7440-43-9]

Presence in Smoke. Cadmium is of particular interest in tobacco because of its uptake from soils (Bache et al, 1987), its relatively high transfer efficiency to mainstream smoke (~60 ng/cigt), and listing by IARC as a human carcinogen. Tobacco like other plants and grains readily takes up cadmium, with cadmium being more readily taken up than other metals like lead. Factors contributing to cadmium's presence in plants is cadmium uptake from soil contaminated with fallout from air and waters used for irrigation, fertilizers such as phosphates (20 mg/kg) and sludge (1500 mg/kg).

Early work on cadmium cited filler levels of 1.4 to 4 µg/g filler, however Bell and Mulchi (1990) found an average of 0.99 µg/g for the top 10 US brands for 1985 with a range of 0.03 to 1.1 µg cadmium per cigarette. Recent work at PM USA R&D by Chang et al found 1.4 µg/g for 1R4F filler and about 1.2 µg/g for a filler made at PM USA Richmond. It would be expected that filler cadmium contents of 1-1.4 µg/g would be typical values. This somewhat lower cadmium content than found in earlier studies is consistent with a trend toward reduced levels in filler, which was mentioned earlier.

It is always important to specify filtration and dilution when evaluating the apparent transfer of cadmium into mainstream smoke as both affect the ultimate transfer. Non-filtered cigarette results were used to evaluate the baseline for cadmium transfer to mainstream smoke. For example, Morgan (1983) found 22% transfer for 2R1 cigarettes. Menden (1972) only reported 7% transfer with an unspecified Kentucky Reference cigarette. Scherer (1983) found considerable variation for German cigarette with an average of about 15% transfer to mainstream.

There has been disagreement as to the distribution of cadmium in mainstream between the particulate phase and gas phase. The most recent results from Nitsch (1989/1991) and Wu (1997) suggest about 95% of cadmium in mainstream smoke is in the particulate phase (63 ng/cig) when compared to the gas phase (3 ng/cig). Cadmium has a high boiling point of 765°C, and is found primarily in the particle phase of mainstream smoke as a product of the exothermic combustion zone where temperatures can reach 700°C to 950°C (Baker, 1975). Cigarette construction effects on mainstream smoke delivery of cadmium were studied extensively by Figueres et al (1994). They found an excellent correlation of design changes (ventilation) to reduce TPM with reduced cadmium in mainstream smoke. Morgan (1983) at PM USA R&D did a smaller study on model cigarettes. He also found a strong effect for dilution. He also noted an apparent further decrease by use of charcoal in a charcoal/CA filter. A PM USA R&D memo from Chang, McDaniel, and Torrence on 16, 11, and 5 mg cigarettes supports this trend of lower cadmium as TPM is reduced. Their filler data was recalculated as cadmium available for transfer (in the length of rod consumed) versus levels in smoke per cigarette:

- 16 mg model transferred 76 ng/cigt to mainstream smoke resulting in 11.7% transfer of cadmium
- 11 mg model transferred 68 ng/cigt to mainstream smoke resulting in 11.3% transfer of cadmium
- 5 mg model transferred 32 ng/cigt to mainstream smoke resulting in 5.8% transfer of cadmium.

Frank Hsu at PM USA RD&E also found an excellent correlation between cadmium and TPM in a large study of commercial cigarettes sold in Massachusetts (personal communication). These results with those reported in the literature, support a range of cadmium transfer for unfiltered cigarettes of about 7-15% and for filtered cigarettes of about 2.5 to 12% filtered cigarettes via the particle phase (Krivan et. al., 1994). Further information on cadmium, with a large compilation of various levels reported for filler and smoke, can be found in a recent review (Smith et al, 1997).

Occurrence in ETS. It should be noted that design features such as dilution, which reduce the mass consumed for mainstream smoke in favor of sidestream smoke may not decrease the absolute level of transfer of cadmium to the sum of both smoke streams (MS + SS). The expectation would be that dilution would divert some material from MS into SS. Nitsch et al (1991) found more cadmium in sidestream (343 ng/cig) than in mainstream smoke (63 ng/cig). For this reason cadmium has been proposed as a possible marker for ETS by Wu et al (1997) although some investigators have not detected cadmium in ETS environments (Benner, 1989).

Known sources other than cigarette smoke. Cadmium is a modern toxic metal, discovered in 1817, with widespread industrial use in the last 50 years according to the American Conference of Governmental Industrial Hygienists (ACGIH, 1999). Cadmium is used in electroplating and galvanizing due to its noncorrosive properties, as a pigment for paints and plastics and as a cathode in batteries. Cadmium is used as a coating for other metals, in bearings, in brazing and low-melting alloys, in nickel-cadmium storage batteries, welding rods, and reactor control rods. Cadmium compounds are employed widely in products such as TV phosphors, pigments in glazes and enamels, dyeing and printing textiles, photography, dry film lubricants, lasers, lithography, plastic stabilizers, semiconductors, pyrotechnics, rectifiers, solar cells, and scintillation counters. Cadmium is a by-product of zinc and lead mining and smelting, which contribute to environmental pollution. Workers in smelters and other metal-processing plants may be exposed to high concentrations of cadmium in the air; however, for most of the population, exposure from contamination of food is most important, secondary to cigarette smoking. Uncontaminated foodstuffs contain less than 0.05 μg of cadmium per gram wet weight, and the average daily intake is about 50 μg (Klassen, 1985). Dietary sources of cadmium include meat, fish and plants (USDA, 1988). High concentrations are found in the liver and kidney of animals and shellfish may be a major source of dietary cadmium containing 100 - 1000 μg/kg (Goyer, 1996). Grains also contain 10 - 150 μg/kg cadmium.

Airborne air from uncontaminated areas contains less than 0.1 $\mu g/m^3$. Respiratory absorption of cadmium is about 15 to 30 percent in industrial situations where cadmium fumes may be present. Total daily intake from food, water and air varies from 10 to 40 μg/day. Smoking one to two packs a day can double the daily intake of cadmium. Dr. Bhattacharyya at Argonne National Laboratory has noted that in highly industrialized countries without pollution controls (i.e. China), with high ambient airborne air concentrations of cadmium, non-smoker blood/urine concentrations may be several times higher than those of smokers in the U.S. (personal communication). The WHO provisional tolerable weekly intake is 7 μg/kg body weight/week for cadmium (WHO, 1992) which is approximate to the weekly intake of a two pack a day smoker.

Toxicokinetics. Gastrointestinal absorption is less than respiratory absorption and is about 5 – 8 percent. Binding to red blood cells and large-molecular-weight proteins in plasma, particularly albumin, transports cadmium in blood. In blood, over 70% of the cadmium is bound to red blood cells. In non-occupationally exposed adults, cadmium levels in blood are usually below 1 μg/100 ml whole blood (median value around 0.15). In all tissues, cadmium is bound mainly to metallothionein. The metal is mainly excreted via the urine and the extent of urinary excretion increases with age. In adults not occupationally exposed to the metal, the level in urine is usually below 1 - 2 μg Cd/g creatinine. Cadmium can also be excreted by other routes (bile, gastrointestinal tract, saliva, hair, and nails), but to a lesser extent than in urine. In man, the two main target organs after long-term exposure to cadmium are the lung and the kidney, though it is generally accepted that the kidney is the critical organ (i.e., the organ that exhibits the first adverse effect). The first detectable adverse effect of cadmium on the kidney

is an increased excretion of specific proteins in urine. About 50 – 75 percent of the body burden of cadmium is in the liver and kidneys; with a half-life of over 10 years in man. Estimates of the average body burden of non-occupationally exposed adults range from 5 to 40 mg. The body burden of smokers is about twice that of non-smokers. The toxicology of cadmium has been extensively reviewed (Friberg, 1986) and (WHO, 1992).

Biological Indicators. Several approaches have been used to evaluate the critical internal dose of cadmium, the dose that under chronic exposure conditions may lead to the occurrence of adverse functional changes in the kidney. It is now possible to measure directly by neutron activation the amount of the metal that has accumulated in the two mains sites of deposition, i.e., the liver and the kidney. However, the evaluation of tissue cadmium *in vivo* by neutron activation is not a routine procedure. Therefore, it is important to evaluate to what extent indirect biological indicators, such as cadmium levels in blood and urine or metallothionein levels in plasma and urine can be used to estimate the internal dose.

The most important measure of recent cadmium exposure is blood cadmium followed by increased urinary cadmium which provides a good index of recent exposure, body burden, and renal cadmium (Lauwerys, 1983). At low exposure conditions (i.e., general environmental exposure or moderate occupational exposure), when the total amount of cadmium absorbed has not yet saturated all the available cadmium binding sites in the organism, the cadmium concentration in urine reflects mainly the cadmium level in the body and hence in the kidney. With an increase in exposure, available cadmium sites (e.g., metallothionein in the kidney) are readily saturated and urinary cadmium excretion becomes a good index of recent exposure. Recent exposure would also be indicated by an increase in blood cadmium with peak concentrations being reached in several minutes and having a half-life of 15 minutes. The relative importance of each factor depends on the intensity of exposure. Thus, in those newly exposed to cadmium, a time lag is observed before cadmium in urine correlates with exposure. This time interval will depend on the intensity of the integrated exposure to cadmium. A highly sensitive assay for blood and urine cadmium (Peterson, 1991) has been miniaturized requiring only 1 ml of fluid with a detection limit of 0.02 µg/L (Bhattacharyya, 2000).

Most of the cadmium in urine is bound to metallothionein, and there is good correlation between metallothionein and cadmium in urine regardless of renal function. Hence, the determination of the level of this protein in urine may provide the same information as the determination of cadmium, but metallothionein analysis presents an advantage over cadmium analysis in that it is not subject to external contamination. A radioimmunoassay has been developed for the determination of metallothionein in urine (Chang, 1980). Further studies are necessary to validate the biological significance of the metallothionein level in plasma.

Confounders. In conducting occupation health surveys and investigating "clusters", hobbies are often found to play a major role in exposure to many compounds. This was often due to the lack of or improper use of required personal protective equipment or industrial hygiene/engineering controls. Many auto body primer paints once contained Cd, although many have been reformulated. A major source of exposure to Cd are woman using enamel glazing for their clay crafts at the local hobby shop. If the kiln is not properly ventilated, high exposures levels may be noted. High concentrations are also noted at landfills permitting burning where improperly disposed Ni-Cd batteries are often accidentally burned. Recent bans on burning and fines for improper disposal of Ni-Cds has help to stem these exposures.

In asking a question as part of an occupation survey, regarding hobbies, one would not specifically ask if a person were exposed to cadmium as they might not know that they have been exposed. Instead, ask for a list of their hobbies and then get more specific on particular use of say paints or enamels ... taking brand and color and date of manufacture, and then checking with the manufacturer as to whether that paint did or did not contain the compound of concern. It was not uncommon to see various chemicals in the home that are out dated older formulations with the suspect chemical. Often cans of paints and pesticides, along with other compounds that had been banned for sale for many years may be found in the home. One of the worst cadmium exposures noted was from an individual whose hobby was loading ammunition and making fireworks. This activity was confined to an enclosed closet about 4 x 3 feet with the door closed. It was very dusty and he was not using dust control or personal protection.
The fax to be sent will include the original paper and the SOT poster abstract for the miniaturized assay.

Medical history may also provide and explanation of other cadmium cofounders. Specifically, renal function should be assessed as renal dysfunction increases the loss of cadmium from the kidney.

In assessing cadmium exposures from cigarette smoking, it is always important to specify amount contained by the cigarette and design effects such as filtration and dilution when evaluating the apparent transfer of cadmium into mainstream smoke as both affect the ultimate transfer.

Recommendations. For the Total Exposure Study (TES), *Determination Of Cadmium In Blood, Plasma And Urine By Electrothermal Atomic Absorption Spectrophotometry After Isolation Anion-Exchange Chromatography* is suggested at described by by David P.Peterson, Edmund A. Huff and Maryka H. Bhattacharyya. (Analytical Biochemistry 192, 434-440, 1991) and further miniaturized by Dr. Bhattacharyya (SOT, 2000). The miniaturized assay overcomes the requirement for a large amount of blood (up to 8 ml). Maryka and Ed Cerny at Argonne National Labs miniaturized assay requires only 1 ml of biological fluid and remains highly sensitive with a detection limit of 0.02 ug/L. This is the only methodology available with enough sensitivity to discriminate between non-smokers, light-smokers, smokers, or changes in smokers with brand switching. Besides sensitivity, the small sample required would also permit time course studies that could not be done routinely with the previous 8 ml sample. Another advantage of the assay is that the first step of adding HCl stabilizes the cadmium while killing blood borne pathogens permitting easy shipment of samples. This would eliminate shipping concerns and interlab variation as all the samples could be sent to one central lab for analysis.

Recommend that Dr. Bhattacharyya be brought in as a consultant to instruct the lab(s) on the use of the assay. Although the assay is very straight forward, technique, equipment selection, and laboratory controls are extremely important to prevent cadmium contamination from other sources. Her lab has been very successful in identifying and eliminating these sources and permitting the full use of the sensitivity that the new methodology provides. Would also recommend that we support her completion of the miniaturization work to permit blood analysis that is important to the TES (Urine has already been validated).

References.

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